THIRTY-FIFTH ANNIVERSARY

STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

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OSWALD T. AVERY, COLIN M. MacLEOD, AND
MACLYN McCARTY

1944-1979

THIS ISSUE OF *The Journal of Experimental Medicine* celebrates the 35th anniversary of its publication of a revolutionary scientific discovery. On February 1, 1944 Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty reported on the chemical composition of the "pneumococcus transforming factor." Biochemical specificity had long been established for proteins and for polysaccharides, and most of the bets about the transforming factor had been on these categories. But the purification process had winnowed those away, and what was left was DNA!

That nucleic acids played a substantial role in the economy of the cell was never in doubt since their discovery by Miescher in 1871. However, it took 73 years to develop a biological assay for the functional role of a nucleic acid. Some biologists even lost hope that genes could function except in the context of an inherently unanalyzable holistic complex. Furthermore, the chemical studies of Phoebus A. T. Levene pointed to a monotonous homogeneity of structure, manifestly inconsistent with the specificity (today we would say informational capacity) of nucleic acids. No wonder that most biologists of that era spoke vaguely of "nucleoproteins" as the most likely composition of genes.

Avery, MacLeod, and McCarty needed to make the most cautious reference to genetics in their paper: whatever speculations they withheld others were quick to supply. There is distressingly little surviving docu-

mentation, but Avery's well known letter to his brother Roy leaves no doubt that he and his group fully appreciated the importance of their contribution for general biology, however specialized their immediate interest in pneumococci.

That the pneumococcus transformation was in some way connected with genetic phenomena was already obvious to Fred Griffith. However, so little was known of the genetics of bacteria that the very use of genetic terminology ("mutation," "gene," "heterozygote," "allele") was controversial. The fact that, for several years, the only marker studied in pneumococcal transformation was polysaccharide synthesis further left room for special pleading, e.g., of chain initiation in some way coupled for DNA and polysaccharide. Within a few years, and largely under the impetus of this paper, doubts about genes in bacteria were rapidly dispelled with newly developed methods of recombination analysis. But only hindsight erases the perplexity that in 1944 surrounded the interpretation of pneumococcus transformation and bacterial genetics generally.

Nor should one fault the initial skepticism that greeted the central claims, viz., of the characterization of DNA. I will at least defend a position I shared though the forties, which was scarcely that the claim was unimportant or wrong: rather, that the issue of the chemistry of the gene was too important to rest on plausible evidence, that it deserved the most critical last-ditch scrutiny lest some lurking protein molecules in part accounted for the biological specificity of "purified" DNA. Recall that Wendell Stanley's first report of TMV crystals described them as pure protein just a few years before!

The critical controversy did indeed clear the underbrush, and it would be barely nine years before Watson and Crick could display the detailed conformational structure of DNA. It was possible that no one would have cared to find out were it not for the discovery announced in 1944. Beyond its details, the revolutionary contribution of Avery, MacLeod, and McCarty was the refocusing on DNA by a generation of chemical biology. Certainly that was its precise impact on the initiation of my own scientific career.

O. T. Avery retired from The Rockefeller Institute for Medical Research in 1948 and died on February 20, 1955 in Nashville, Tennessee. Colin MacLeod served on the scientific staff of The Rockefeller Institute from 1934 to 1941, whence he became professor of microbiology at New York University Medical School. He died on February 12, 1972, in London. Maclyn McCarty, the junior and surviving author, is John D. Rockefeller

Jr. Professor at The Rockefeller University having also served as Vice President from 1965 to 1978 and as Physician-in-Chief of The Rockefeller University Hospital from 1960 to 1974. The occasion of this republication is also a celebration in his honor, to be held at the University on February 2, 1979. We are all looking forward to his own memoir that may eventually offer the intimate story of the most seminal discovery of twentieth-century biology.

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